Modeling Bone Remodeling

Studying Bone Dynamics with Monte Carlo Codes

by Vin LoPresti

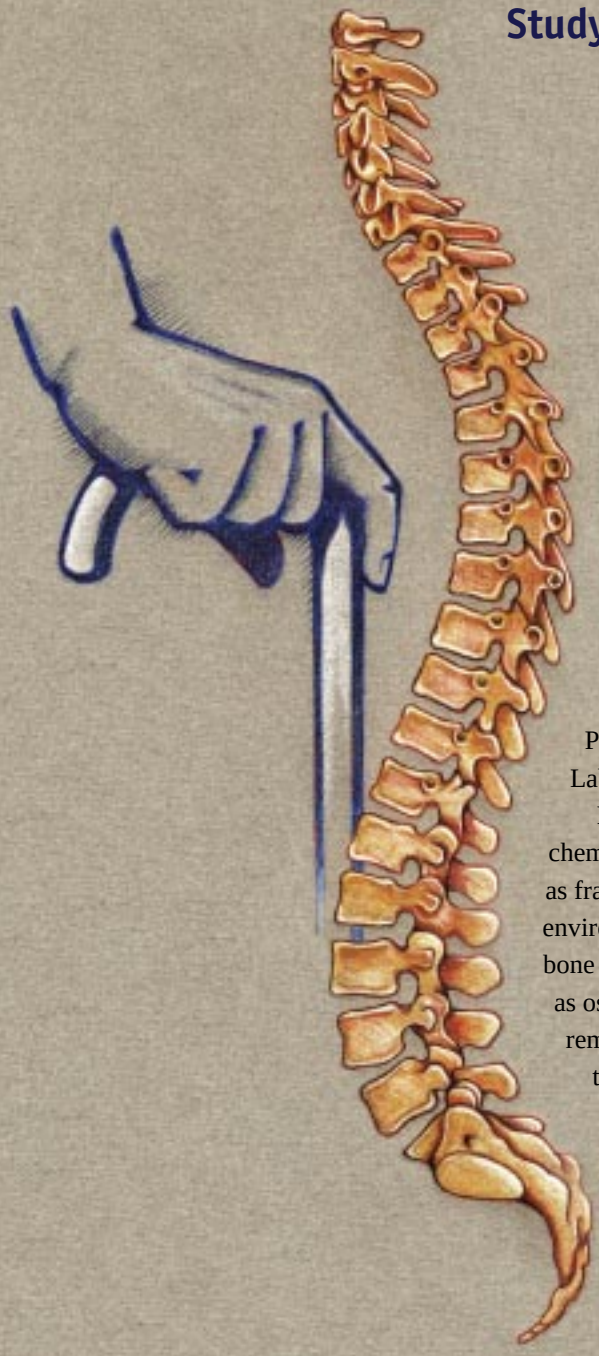


Illustration by Donald Montoya

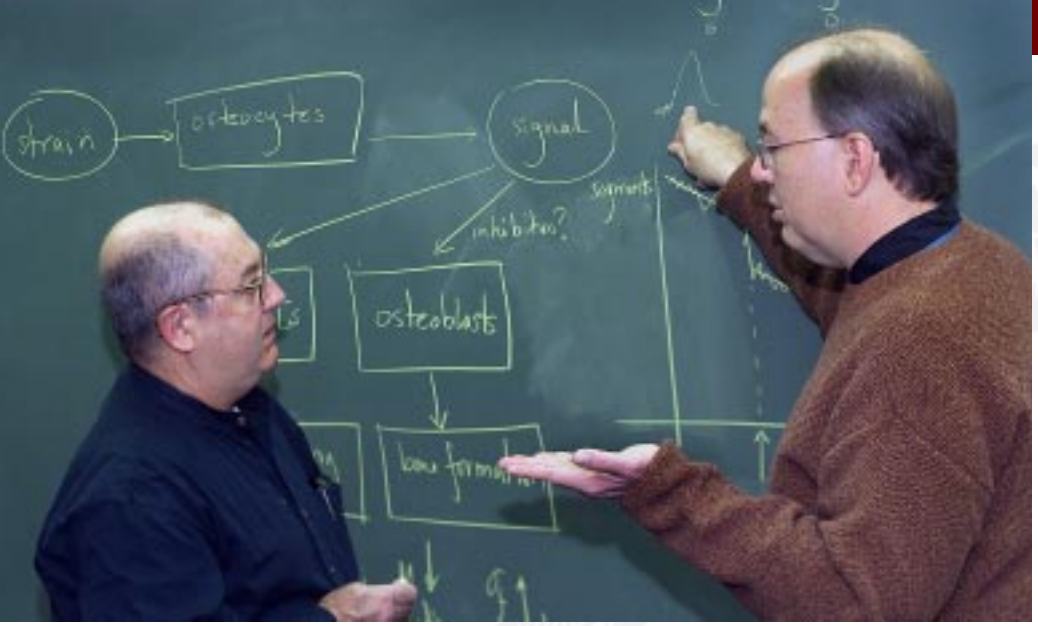
Often viewed as static support beams, human bones are in fact dynamic organs enmeshed in the network chatter—the complex information processing—that characterizes human physiology. Continually remodeling through processes that remove existing bone and deposit new bone, a young adult's skeleton replaces one-fifth of its bone tissue each year.

This dynamic remodeling serves both to subtly adjust structure in response to changing stresses and to maintain the proper level of blood calcium, a mineral essential to the functioning of all cells. To create more informative—and ultimately more medically useful—models of bone dynamics, a team from the Theoretical and the Applied Physics Divisions is drawing on time-tested algorithms and the Laboratory's supercomputing capability.

Remodeling normally occurs during bone growth, in response to physico-chemical factors such as stresses from exercise, during repair of injuries such as fractures, and during hormonal changes. Remodeling includes the sensing of environmental changes, the formation of new bone, and the removal of existing bone ("resorption"). Because of bone remodeling's complexity, illnesses such as osteoporosis—which result from disturbances in the control of remodeling—are poorly understood. Existing treatments for such illnesses therefore relieve symptoms rather than address underlying causes. To firmly ground their research in the real world of biomedicine, the Los Alamos team is collaborating with a local orthopedic surgeon, Wayne Augé.

Modeling Complex Systems

The team is using simulation techniques that have proved valuable in materials science, mechanical engineering, chemistry, and physics and that were originated at the Laboratory during the 1950s by Nicholas



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Investigators Antonio Redondo and Richard LeSar discuss a modeling strategy.

Metropolis and his collaborators. Exemplified by the well-known Monte Carlo method, these computational approaches lend themselves to analyzing any complex system that exhibits multiple states and nonlinear competing interactions.

Since biological systems are characterized by multistate nonlinearity, they are amenable to Monte Carlo analysis. Moreover, enough is known about the competing processes in bone remodeling to make it a logical candidate for study. Monte Carlo methods tend to find preferred paths for a system's evolution of states, ignoring irrelevant ones. They are, therefore, well suited for modeling living systems, which clearly cannot "visit" any chemical configuration that would be incompatible with continued life.

Honing In on Bone

In some respects, bone tissue closely resembles reinforced concrete: its hard, inflexible calcium phosphate matrix is reinforced by flexible fibers of collagen, a protein that plays a role similar to that of steel "rebars." However, bone matrix is also quite different from concrete in that it is populated by three types of living cells and crisscrossed by blood vessels. This dense cellularity and blood supply enable bone to renew its components at a microscopic level—by resorbing existing bone and forming new bone—while remaining stable at the macroscopic level. Such processes of self-renewal are characteristic of all living tissue. In bone, they are carried out by a grouping of three varieties of bone cells collectively referred to as a basic multicellular unit, or BMU (see the sidebar on page 12 for details).

Bones are also organs whose design incorporates the best in biological engineering know-how. Although on their exterior surfaces, bones appear to be solid matrix with few interruptions, this so-called compact bone is merely a shell. For under the surface, most bones resemble a rigid sponge, a meshwork of thin beams of bone tissue. Such an arrangement is analogous to the exterior-wall construction of homes—internally composed of regularly spaced studs, externally faced with particle-board sheets. This design in both houses and bones confers strength while minimizing weight.

Osteoporosis

Osteoporosis results from an imbalance in which bone resorption outstrips bone formation. The net loss of bone matrix renders bones weaker and more susceptible to fracture, with the fracture risk doubling for every 10 percent bone loss. Well known as an illness of older women, osteoporosis is also on the rise for men.

The effects of osteoporosis are most readily seen in x-rays of the spongelike interiors of bone. The erosion or thinning of the individual beams of this rigid meshwork is both an important clinical indicator and a key mechanical problem, weakening weight-bearing bones and predisposing them to fracture and collapse. Just as progressive termite damage to the supporting studs in a house's wall will eventually produce disastrous results, so too will the erosion of this spongy bone tissue.

Modeling Bone Dynamics on Three Levels

Because of the complex signaling network that regulates bone cells, counteracting illnesses such as osteoporosis or the bone losses accompanying cancer requires an improved ability to predict how changes in that network will affect the physical composition of bones. From signaling substances referred to as "bone morphogenetic proteins" to immune-system inflammatory proteins to hormones like estrogens, there are many signaling configurations to which bone cells respond.

In addition, any set of signals will produce not only a physiological response (such as remodeling) but also feedback signals that tend to modulate the effect of the initial signals. Factor in information communicated locally among neighboring bone cells, and the need to use high-performance computers to model such interactions becomes obvious. Therefore,

developing computational models of signaling is a core focus of this research.

The microscopic scale of the BMU comprises the first level of the team's modeling. The model incorporates the three BMU bone cells, the signaling molecules by which they interact, and known triggers of remodeling such as altered stress on a bone. All interactions between pairs of cells are written in the general form used to describe a chemical reaction: $A + B \rightarrow C + D$, where A + B describes the particular interaction and C + D, the outcome of that interaction. The entire set of such "reactions" constitutes the input to the model. The algorithms that solve the equations by predicting most-probable BMU behaviors are identical to those developed to study the progress of chemical reactions.

A second modeling level examines the effects of many BMUs reshaping the individual beams of spongy bone. Model parameters include rates of BMU activation and of bone resorption and formation. Using a Monte Carlo sampling allows researchers to examine

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Dr. Wayne Augé, an orthopedic surgeon from Española, NM, is helping the team sort through contradictory experimental findings in bone-research literature. His experience should prove invaluable in evaluating the team's choices for configuring its models.

Bone Structure and Osteoporosis

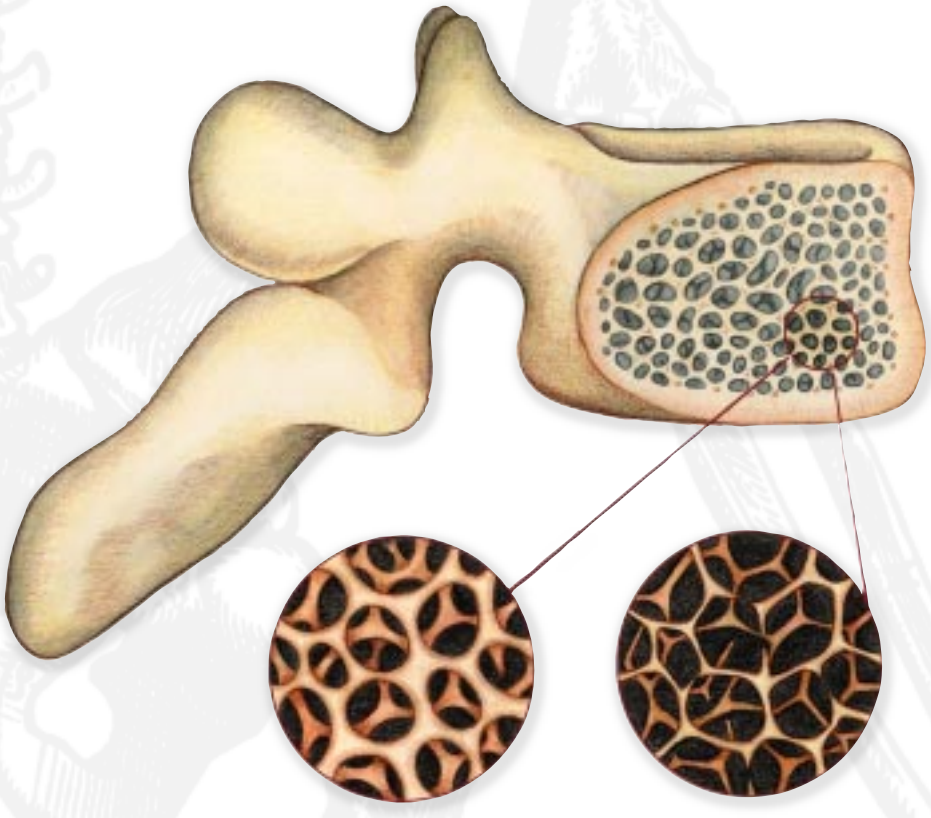
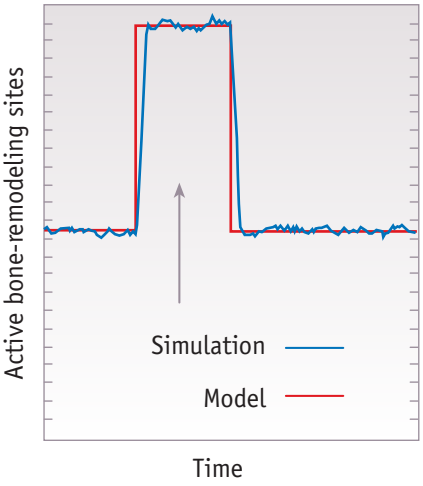


Illustration by Donald Montoya

This drawing of a spinal vertebra illustrates the exterior shell of compact bone with its interior beams of bone—a meshwork akin to a rigid sponge. The magnifications of this so-called spongy bone show a typical appearance for normal anatomy (left) and the thinner and incomplete beams of bone seen in osteoporosis (right). Such bone loss weakens the weight-bearing capacity of vertebrae, potentially leading to their compression and the "shrinking," or abnormal curvature, of the entire spine over time. In addition, all osteoporotic bones demonstrate an increased propensity to fracture, often described as brittleness.



An analytical model developed by the investigators closely coincides with their Monte Carlo simulation in describing the increase in bone remodeling that occurs during menopause (arrow).

Bone-Remodeling Dynamics

Bone dynamics encompass a continuous building up and tearing down (resorption) of bone matrix. This ongoing remodeling results from the interplay of three bone cell types collectively referred to as a basic multicellular unit, or BMU.

Osteocytes live in fluid-filled hollows within the bone matrix and are interconnected by fingerlike extensions through microscopic tunnels. They are believed to be the cells that sense mechanical strain—either piezoelectrically through ionic currents induced when bone is deformed or by detecting fluid flow in the tunnels. Osteocytes are presumed to respond to this strain by sending signals that either cause new bone formation or existing bone removal.

A second bone cell, the osteoblast, is responsible for forming and depositing new matrix. A third cell, the osteoclast, is charged with resorbing bone matrix by dissolving its calcium and phosphate and releasing them into blood. Much as acid rain increases the weathering of rocks, so osteoclasts create an acidic microenvironment that is necessary to dissolve bone minerals and to activate enzymes that break down collagen fibers.

Both osteoclasts and osteoblasts play a role in the repair work that follows fractures. The net gain or loss of bone depends on a delicate balance between the activity and number of these two cell types. When osteoclasts remove bone more rapidly than osteoblasts create new bone, a net bone loss occurs. For example, when muscle-generated mechanical stress is abnormally low, such as for a bedridden person, there tends to be an overall loss of bone from the skeleton. This is likewise a problem for astronauts, for whom extended weightlessness greatly diminishes the natural mechanical stress produced when muscles hold the skeleton upright against the force of gravity.

NASA

In a talk at Los Alamos, astronaut and physician Jerry Linenger said that during his four months in space, he lost 13 percent of his bone mass (enough to more than double his probability of bone fractures). Linenger also reported that after a year of vigorous musculoskeletal-stressing exercise such as swimming, he had regained only half the lost bone mass. These numbers emphasize the importance of physical activity in maintaining healthy bones.

how variations in these parameters affect the overall bone density, for example, during menopause.

Building on the work of others, the investigators have also developed an analytical model that describes the decrease in bone density characterizing menopause. Their two-equation model is in agreement both with the results of the simulation and with experimental observation. However, it yields rapid solutions as compared with the time-consuming simulations and permits a deeper understanding of the relationships among the variables governing remodeling.

The team's third level of bone modeling will examine how changes in bone structure (such as BMU reshaping) affect bone's mechanical properties. This study will use the finite-element method to examine the response of large pieces of bone to macroscopic external stresses.

The finite-element method is commonly used in industrial applications such as modeling the crashworthiness of automobiles and designing commercial aircraft. The key to using the method is to know the properties of the relevant materials. Since bone's mechanical properties are clearly linked to the porosity of its internal rigid-sponge structure and since previous model levels characterize this porosity, the finite-element method should prove a fruitful approach. During this study, the calculated mechanical properties will be validated by comparing them with experimental data.

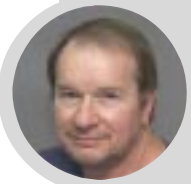
Human Health and Beyond

Funded by a Laboratory Directed Research and Development grant, the team's research is congruent in several ways with the Lab's vision to "serve the nation by applying science and technology to make the world a safer and better place to live." In addition to its implications for more efficacious treatments of osteoporosis—an illness threatening millions of Americans—the research is also relevant to materials development. Imagine a new material that, like bone, could respond to environmental changes by altering its properties to maximize functionality and minimize the probability of failure under extreme conditions. Previously the stuff of animated cartoons, such a vision has far more pragmatic significance for these Los Alamos researchers. ■

The Researchers

Antonio Redondo received an M.Sc. and a Ph.D. in applied physics from the California Institute of Technology. Before joining the Laboratory, he served as an associate professor of physics at the Universidad de Los Andes in Venezuela.

Richard LeSar holds an A.M. in physics and a Ph.D. in chemical physics from Harvard. He serves as adjunct professor at the University of California, Santa Barbara. In addition to simulation methods, he has broad research experience in the area of material microstructure.



William Wray holds a B.S., M.S., and Ph.D. in aerospace engineering and engineering mechanics from The University of Texas. His bioengineering research includes a patent for a noncontact method of determining intraocular pressure.

Yi Jiang received a Ph.D. in physics from Notre Dame after earning a B.S. in physics in China. In addition to biophysics, her research interests include soft condensed matter and complex fluids.

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